REMARKS

Status of the Claims

Claims 4-10 and 15-16 are currently pending. Claims 1-3, 11-14 and 17-24 are cancelled. Claims 4, 7, and 10 are currently amended. No new matter is added by these amendments; only minor corrections were made to the claim structure, for example in claim 7 changing "a" to "the", and in claim 10 removing the word "fluorescent".

Applicants respectfully request entry of the present amendments.

Claim Rejections – 35 U.S.C. §112

The Examiner has rejected claim 10 under 35 U.S.C. §112, second paragraph.

Applicants have amended claim 10 to remove the term "fluorescent", correcting the antecedent basis to "the first label and a second label" according to claim 8.

Applicants respectfully request withdrawal of the rejection of claim 10.

Claim Rejections – 35 U.S.C. §103

The Examiner has rejected claims 1, 4, 5, and 8-10 under 35 U.S.C. §103(a) as being unpatentable over Schmidt et al. in view of Hemauer et al., and further in view of Buck et al. (Final Action pages 2-3) The Examiner asserts, in part, that one of ordinary skill in the art would have been motivated to modify the method of Schmidt to use the oligos of the instant invention because Schmidt demonstrates the benefits of designing and using similar oligos targeting the NS1 region, and because Hemauer also amplifies the NS1 region, and further because Buck demonstrates the capability of multiple primers to equivalently amplify the same target region. (Final Action pages 6-7)

Further, the Examiner has rejected claims 1, 4-7, 9 and 10 under 35 U.S.C. §103(a) as being unpatentable over Harder et al. in view of Hemauer et al., and further in view of Buck et al. (Final Action pages 7-8) The Examiner has rejected claim 15 under 35 U.S.C. §103(a) as being unpatentable over either one of Schmidt et al. in view of Hemauer et al. and Buck et al. (as applied above to claims 1-5 and 8-14) OR Harder et al. in view of Hemauer et al. and Buck et al. (as applied above to claims 1-7, 9, and 10-14 and further in view of Andrus et al.). (Final Action page 13) And, the Examiner has rejected claim 16 under 35 U.S.C. §103(a) as being unpatentable over either one of Schmidt et al. in view of Hemauer et al. and Buck et al. (as applied above to claims 1-5 and 8-14), OR Harder et al. in view of Hemauer et al. and Buck et al. (as applied above to claims 1-7, 9, and 10-14) and further in view of Mosquera et al. (Final Action pages 13-14)

Applicants respectfully traverse the rejections. None of the cited references teach the sequences, or the combination of these sequences, as provided in the instant claims.

The Examiner states: "Schmidt discusses primers and a probe that are nearby to such sequences as the instant SEQ ID NOs: 11, 15 and 17 and are located within the same NS1 region of the Parvovirus B19 genome." (Final Action page 4). Further, the Examiner states that Hemauer identifies the NSC1 region and "also teaches nearby primers to amplify this region (see Table 2 on Page 1783)." (Final Action page 4) Similarly, the Examiner states that Harder teaches primers and probes that are "nearby" to the sequences of the instant invention. (Final Action page 9)

However, it is critical to note that the NS gene spans 2 KB which is a large stretch of sequence; a primer that binds tens or hundreds of bases away from another primer is by no means considered "nearby" as asserted by the Examiner.

The following table summarizes the NS region oligos as taught by Schmidt (page 229 last paragraph) and Hemauer (Table 2), in comparison to the oligos as provided in the instant invention:

	Claims	Schmidt	Hemauer
Upstream primer/ location	SEQ ID NO: 15 2044-2064	TP1 2030-2048	F1 1817-1833
	Comparison to claimed SEQ:	*15 bases away* *5 bases (25%) overlap*	*211 bases away*
Downstream primer/ location	SEQ ID NO: 17 2193-2174	TP2 2171-2151	B1 2500-2517
	Comparison to claimed SEQ:	*23 bases away*	*307 bases away*
Probe/ location	SEQ ID NO: 11 2070-2095	Probe 2050-2073	(NA)
	Comparison to claimed SEQ:	*22 bases away*	*na*

Similarly, Harder Table 1 provides sequences that are directed to the NS region positions 1420-1631. These sequences are greater than 400 bases away from the sequences of the instant invention.

Applicants assert that the sequences of the instant invention are not simply located "nearby" the sequences of Schmidt, Hemauer or Harder. There is no motivation provided in either Schmidt, Hemauer or Harder to make primers in different locations of the NS gene other than the specific locations presented in their publications; neither Schmidt nor Hemauer nor Harder discuss the need to improve or change the sequences provided. In fact Hemauer teaches the amplification of 4 distinct regions of the genome, not just NS, and does not provide evidence that one particular region should be selected away from the other 3 to detect parvovirus.

The Examiner asserts that Hemauer teaches a conserved stretch of sequence at position 2020-2240, therefore one of skill would recognize that amplification and detection of such a conserved region would allow for detection of parvovirus. (Final Action page 7 and page 12) Applicants assert that Hemauer provides that this amplification region is only "relatively conserved" in contrast to some of the other regions discussed. This "conserved" region showed 12 exchanges, or base differences, in the limited sample set provided (only 20 patients). Applicants note that Hemauer's own NS oligos are designed OUTSIDE of this supposedly "conserved" region. Hemauer also provides that "the region from nt 2985-3170 was highly conserved, and only a few nucleotide changes could be identified (3 in 185 bp)." (Hemauer page 1784, top of right column) Hemauer goes on to teach that other regions had even less exchanges when described at a protein level, and that changes are not equally frequent within all isolates. Additionally Hemauer notes that "all isolates exhibited changes in their DNA sequences". (Hemauer page 1783 right column). No statistical analysis is provided showing if any of these base differences are even significant in this small sample size. Applicants assert that the Examiner is in error in drawing the conclusion from the limited data set in Hemauer that position 2020-2240 is the most conserved region of the parvovirus genome. In fact, based on the relatively low number of base changes found in region 2985-3170, Hemauer teaches away from using the NS region because one of skilled in the art would have had a greater motivation to design primers in the 2985-3170 region than in the NS region.

Applicants respectfully assert that one of ordinary skill in the art would NOT have been motivated to modify the method of Schmidt simply because of the fact that Hemauer and/or Harder also amplifies the NS1 region. This region spans > 2KB which offers thousands of possible alternative oligo sequence design options. The specific combination of

SEQ ID NOs 11, 15 and 17 as taught by the instant invention provides for the detection of a target nucleic acid comprising the sequences of parvovirus B19 in a sample. The Examiner has not cited any additional art that would motivate one of ordinary skill to design the specific oligonucleotides or combination thereof as presented in the instant invention.

The Examiner asserts that the claimed primers and probe simply represent structural homologs, or "equivalents", which are derived from sequences suggested by the prior art. (Final Action page 5) Applicants assert that the Examiner is in error in citing MPEP 2144.06 because the term "structural homolog" in the context of nucleic acid sequences refers to a "degree of similarity between the sequences" and NOT the fact that they can hybridize to the same virus. As discussed above, the art cited by the Examiner provides sequences which are different than and completely distinct from the sequences provided in the instant invention. Oligonucleotides that bind to the same gene tens or hundreds of bases apart are NOT homologs.

An example of homologs in the context of a nucleotide sequence would be two oligonucleotides such as illustrated below:

1) 5'-AACATTGGCTAAAAGCTTAA-3'
2) 5'-ATTGGCTAAAAGCTTAACGC-3'

These 2 oligonucleotides have similar properties in that they would hybridize to the same sequence area, since they have the same 17 of 20 bases (85%) and share a structural similarity. In this case, based on sequence 1) a biochemist of ordinary skill in the art may be motivated to design "homologous" sequence 2).

However, the oligonucleotides of the instant invention do not share such similar properties with the sequences provided in the prior art. All but 1 of the sequences of the instant invention have zero homology to the sequences of the cited prior art; SEQ ID NO: 15 has a 25% match to Schmidt primer TP1. This 25% match represents only 5 base pair similarity, and one skilled in the art would recognize that 2 sequences with such a low similarity would not be considered "homologous". As discussed above, the parvovirus NS1 region is greater than 2 KB. Oligonucleotides that bind to different parts of this 2000 base pair region are definitely NOT "equivalents". The Examiner has over-generalized the terms of homologs and/or equivalents in the present context of nucleic acid amplification.

With regard to the issue of reasonable expectation of success in using such alleged equivalents, the Examiner asserts that Buck provides evidence. (Final Action page 5) Applicants assert that the Examiner is in error in citing Buck to prove equivalence of

primers. Buck is not a relevant example in the design of primers to highly variable viral sequences provided at potentially low abundance. The primers of Buck are designed to amplify sequences from plasmids which are found in high abundance in the reaction and have 100% sequence identity. Buck acknowledges that a plasmid template was selected for this study because of its "lack of obstacles.... The template was extremely pure and optimal for sequencing.... Different results may be obtained using less carefully purified DNA templates with unusual sequences or structure or in less rigorous controlled sequencing operations." (Buck Discussion, pages 535-536) Buck acknowledges a reduced expectation for success when working with a less controlled template sequence. Applicants respectfully assert that in the context of a highly sequence-variable template, provided at a potentially low abundance such as parvovirus as discussed throughout Hemauer for example, one skilled in the art would recognize that the expectation for success in designing effective primers would significantly decline. The expectation for success would instead become a less predictable "hope to succeed". Applicants assert that the Examiner has not provided a reasonable expectation of success in citing Buck to allege equivalence of primers.

Applicants respectfully assert that one of ordinary skill in the art would NOT have been motivated by the teachings of the cited prior art to arrive at the instant invention for the reasons stated above. The combination of the cited prior art does not teach all of the elements of the instant claims, specifically SEQ ID NOs. 11, 15 and 17 and the combination thereof. None of the art cited by the Examiner in addition to Schmidt, Hemauer, Harder and Buck make up for the deficiencies in disclosing the claimed elements. The Examiner has not provided specific citations in the prior art which provide a recognized problem or need to design different sequences than as provided in the prior art; there is no motivation for one of skill in the art to alter the sequences as taught by the prior art to achieve the claimed invention when the provided sequences already serve their intended function. Lastly, the Examiner has not established equivalency or a reasonable expectation of success in the citation of Buck, as discussed above.

Therefore, the Examiner has not presented a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the §103(a) rejections.

CONCLUSION

Applicants respectfully request entry of the present RCE and remarks. In view of the above, Applicants believe all claims now pending in this Application are in condition for allowance. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-730-8566.

The commissioner is hereby authorized to charge the amount of $810, the fee pursuant to 37CFR §1.114, to Deposit Account No. 50-0812. Applicants assert no further fees are due, however please grant any additional extensions of time that may be required to enter this amendment and charge any additional fees or credit any overpayments to Deposit Account No. 50-0812.

Please direct all future correspondences to: Customer No. 22829.

Respectfully submitted,

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